sTWEAK– A Potential Biomarker for Predicting Response and Long-Term Outcomes to MUC1-specific Cancer Vaccine in Early Breast Cancer Patients – A translational study of the ABCSG-34 trial.

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Introduction

Soluble Tumor Necrosis Factor-related Weak Inducer of Apoptosis (sTWEAK), Vascular endothelial growth factor A (VEGF-A), soluble Programmed cell death 1 ligand 2 (sPD-L2), and Osteoprotegerin (OPG) were analyzed for their prognostic and predictive value in women with early-stage HER2-negative breast cancer who received neoadjuvant chemotherapy or endocrine therapy, and were randomized 1:1 to additional mucin 1 (MUC1)-based immunotherapy (L-BLP25).

Methods and Materials

Baseline plasma biomarker levels were assessed in 314 patients from the prospective, randomized, open-label, two-arm phase II ABCSG-34 trial. Of these, 240 received chemotherapy and 74 endocrine therapy, with (n = 160) or without (n = 154) a MUC1 antigen-specific peptide vaccine. Treatment response was evaluated by residual cancer burden (RCB 0–III) and pathologic complete response (pCR). Long-term outcome data for invasive disease-free survival (iDFS), overall survival (OS), and distant recurrence-free survival (DRFS) were available in 227 patients (see Figure 1.). Associations of $\log_2$-transformed biomarkers with response and survival were analyzed using ordinal logistic regression and Cox models, including interaction terms to test predictive effects and to determine optimal cut-offs. Patient characteristics are shown in Table 1.

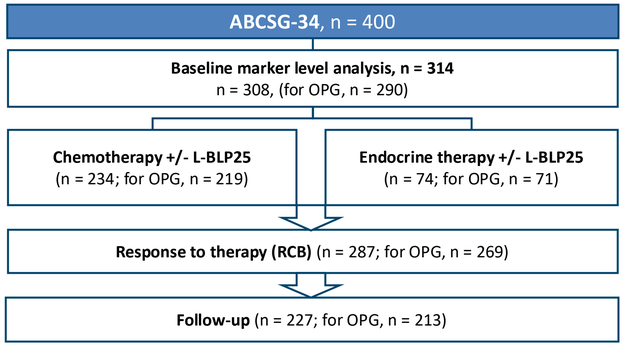


Figure1. Flowchart describing the clinical study design, number of patients and sample dataset overview.

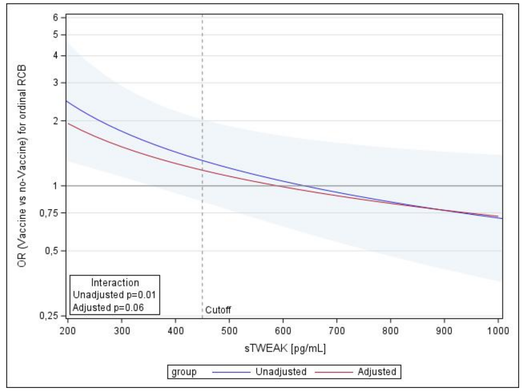


Figure 2. Effect trend plot for sTWEAK including the optimal cut-off at 450 pg/mL.

	Chemotherapy		Endocrine Therapy	
	Analysis set (n=240)	ABCSG-34 (n=311)	Analysis set (n=74)	ABCSG-34 (n=89)
Age				
mean (SD)	48.8 (10.9)	49.3 (11.0)	66.9 (7.4)	67.1 (7.3)
cT-stage				
T1	66 (27.5%)	86 (27.7%)	35 (47.3%)	39 (43.8%)
T2	145 (60.4%)	189 (60.8%)	35 (47.3%)	43 (48.3%)
T3	24 (10.0%)	31 (10.0%)	3 (4.1%)	4 (4.5%)
T4	5 (2.1%)	5 (1.6%)	1 (1.4%)	2 (2.2%)
missing	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)
N-stage				
cN+	98 (40.8%)	126 (40.5%)	15 (20.3%)	19 (21.3%)
cN-	136 (56.7%)	178 (57.2%)	59 (79.7%)	70 (78.7%)
missing	6 (2.5%)	7 (2.3%)	0 (0%)	0 (0%)
Grading				
G1	1 (0.4%)	2 (0.6%)	15 (20.3%)	15 (16.9%)
G2	67 (27.9%)	82 (26.4%)	52 (70.3%)	63 (70.8%)
G3	162 (67.5%)	212 (68.2%)	4 (5.4%)	4 (4.5%)
missing	4 (1.7%)	5 (1.6%)	0 (0%)	0 (0%)
Cancer type				
HER2+	1 (0.4%)	1 (0.3%)	0	0
HR+/HER2-	129 (53.8%)	174 (55.9%)	74 (100.0%)	89 (100.0%)
TNBC	104 (43.3%)	130 (41.8%)	0	0
missing	6 (2.5%)	6 (1.9%)	0	0
RCB score				
0	60 (25.0%)	73 (23.5%)	2 (2.7%)	2 (2.2%)
I	26 (10.8%)	34 (10.9%)	8 (10.8%)	12 (13.5%)
II	99 (41.3%)	135 (43.4%)	45 (60.8%)	51 (57.3%)
III	37 (15.4%)	47 (15.1%)	16 (21.6%)	20 (22.5%)
missing	18 (7.5%)	22 (7.1%)	3 (4.1%)	4 (4.5%)

Table 1. Patient characteristics of the analysis set as well as the original ABCSG-34 trial.

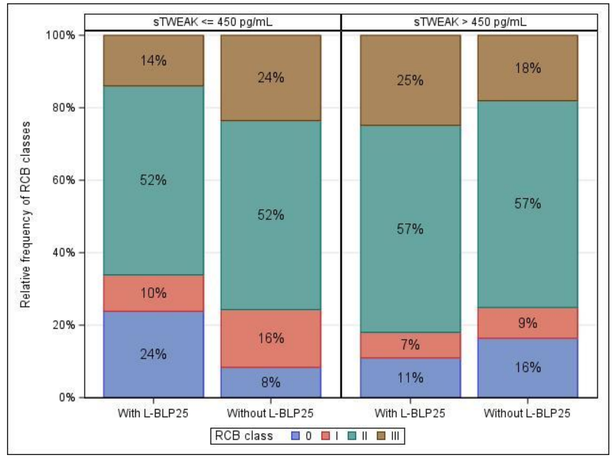


Figure 3. Predicted RCB class probabilities derived from a non-proportional odds logistic regression model

Results

sTWEAK levels were associated with vaccine benefit regarding RCB (interaction p=0.01), with a predictive cut-off of 450 pg/mL (Fig.2 and 3). Patients with low sTWEAK had higher odds of favorable RCB with vaccination (OR 2.12; 95% CI 1.24–3.64), whereas high sTWEAK patients showed no benefit (OR 0.63; 95% CI 0.30–1.32; c-index = 0.64; Fig. 2.). VEGF A, sPD-L2, and OPG were not associated with response. After a median follow-up of 7.2 years, 81 iDFS, 53 OS, and 62 DRFS events occurred. Low-sTWEAK patients receiving tecemotide exhibited improved 7-year rates of iDFS (72% vs 58%, HR 0.61), OS (86% vs 66%, HR 0.43) and DRFS (84% vs 61%, HR 0.36). However, high-TWEAK patients showed no benefit (Fig. 4). Possibly due to limited event numbers, subgroup effects lacked statistical significance (interaction p=0.63, p=0.26, and p=0.14).

Conclusions

Low baseline sTWEAK levels are associated with improved RCB response to neoadjuvant MUC1 immunotherapy, supporting the potential utility of sTWEAK as a predictive biomarker and underscoring the need for validation in larger cohorts.

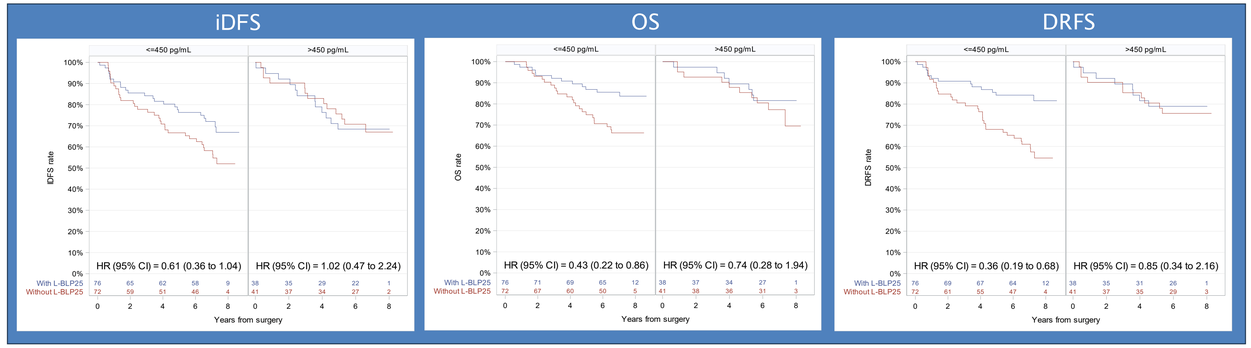


Figure 4. Survival curves in patients stratified by sTWEAK cutoff value. Kaplan–Meier curves illustrating invasive disease-free survival (iDFS), overall survival (OS), and distant recurrence-free survival (DRFS).

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